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# Lipid abnormalities associated with urinary albumin excretion rate in Taiwanese type 2 diabetic patients

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**Lipid abnormalities associated with urinary albumin excretion rate in Taiwanese type 2 diabetic patients.**

*Background.* The purpose of this study was to examine the lipid abnormalities associated with urinary albumin excretion rate (UAER) in type 2 diabetic patients.

*Methods.* A total of 275 (122 men and 153 women; aged 60.6 ± 11.1 years) patients were selected with stringent criteria to prevent confounders. Normoalbuminuria ($N = 152$) and albuminuria ($N = 123$) were defined as urinary albumin-to-creatinine ratio (ACR) of <30 and ≥30 μg/mg, respectively. Total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, and apolipoproteins A1 (ApoA1) and B (ApoB) were measured and non-HDL cholesterol calculated. The subjects were divided into four phenotypes based on triglycerides (<1.5 or ≥1.5 mmol/L) and ApoB (<1.2 or ≥1.2 g/L).

*Results.* Total cholesterol, ApoB, and non-HDL cholesterol were significantly ($P < 0.05$) higher in patients with albuminuria. For quartiles of the lipid parameters, prevalences of albuminuria showed significant association with ApoB and non-HDL cholesterol ($P$ trend <0.05). After adjusting for age, systolic blood pressure and hemoglobin $A_{1c}$ ($HbA_{1c}$) correlation coefficients between the natural logarithm (ln) ACR and lipid parameters, odds ratios for albuminuria, and standardized regression coefficients for ln ACR, were significant for total cholesterol, ApoB and non-HDL cholesterol in all subjects and in men, but only ApoB was significant in women. For patients with normoalbuminuria, frequencies of normotriglycerides/normo-ApoB, hypertriglycerides/normo-ApoB, normotriglycerides/hyper-ApoB, and hypertriglycerides/hyper-ApoB were 44.7%, 28.9%, 10.5%, and 15.8%, respectively; and were 30.1%, 19.5%, 15.4%, and 35.0% for patients with albuminuria ($P <$ 0.001). The respective adjusted odds ratio for albuminuria for the four phenotypes was 1.00, 1.04 (0.54 to 2.00), 2.25 (1.02 to 5.00), and 3.38 (1.75 to 6.53).

*Conclusion.* Increased UAER is associated with ApoB-containing lipoproteins and the phenotype of hypertriglycerides/hyper-ApoB is associated with the highest risk of albuminuria. The surrogate marker of non-HDL cholesterol for ApoB is more applicable to the diabetic men.

**Key words:** microalbuminuria, lipid profile, apolipoprotein B, non-HDL cholesterol, type 2 diabetes.

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Increased urinary albumin excretion rate (UAER), even in the early microalbuminuric range, is associated with progressive renal failure and increased cardiovascular morbidity and mortality in diabetic and nondiabetic patients [1–8]. The mechanisms linking increased UAER and increased risk of cardiovascular disease remain to be answered, but one of the mechanisms is its link with atherogenic lipoproteins. Although lipid metabolism has been extensively investigated in diabetes, little information is available concerning the lipid abnormalities associated with increased UAER, especially in the early stage without impairment in renal function. In a prospective study from the Steno Diabetes Center, the baseline total cholesterol but not high-density lipoprotein (HDL) cholesterol was an independent risk factor for microalbuminuria and overt diabetic nephropathy in type 2 diabetic patients [9]. However, apolipoprotein (Apo) levels were not measured in that study. Samuelsson et al reported that ApoB was associated with a declining glomerular filtration rate (GFR) [10], and that renal dyslipidemia was predominantly associated with the accumulation of ApoB-containing lipoproteins in both sclerotic and nonsclerotic glomeruli [11]. However, these studies evaluated patients with more advanced renal disease and not specifically in diabetic patients. A Japanese study showed that type 2 diabetic patients who progressed from normoalbuminuria to microalbuminuria after 2 years had significantly higher baseline triglycerides and ApoB levels [12]. However, this study did not evaluate the interaction between triglycerides and ApoB.

Assessments of the conventional lipid profile including total cholesterol, triglycerides, HDL cholesterol and low-density lipoprotein (LDL) cholesterol do not always appropriately reflect the atherogenicity associated with dyslipidemia in the diabetic patients. Instead, measurement of plasma ApoB may reflect the total number of

atherogenic lipoprotein particles, including very low-density lipoprotein (VLDL), LDL, intermediate-density lipoprotein (IDL), and lipoprotein(a) [13]. Because ApoB is not always measured in clinical practice, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) recommended the calculation of non-HDL cholesterol as a surrogate marker [14]. However, Sniderman, Scantlebury, and Cianflone [15] suggested that lipid measurement should include ApoB (rather than the surrogate non-HDL cholesterol) and patients should be classified based on triglyceride and ApoB levels because hypertriglyceride/hyper-ApoB phenotype is more atherogenic and is characterized by high triglyceride, low HDL cholesterol and increased numbers of small, dense LDL particles [15]. To the best of our knowledge, whether this phenotype is associated with increased UAER in type 2 diabetic patients has not been examined. Therefore, the objective of this study was to evaluate the relationship between UAER and the measured lipid profile, including total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ApoA1, and ApoB, the calculated non-HDL cholesterol, and the phenotype of hypertriglyceride/hyper-ApoB in type 2 diabetic patients.

## METHODS

### Subjects

The study was approved by the Department of Health, Executive Yuan, Republic of China with subjects participating voluntary with their informed consent. In a diabetic clinic at the National Taiwan University Hospital, the demographic data and basic information of the patients have been collected for convenience of follow-up, when they attended the clinic for the first time. Among them, there were 777 diabetic patients (339 men and 438 women) aged 30 years or older with the diagnosis of type 2 diabetes mellitus. The patients were treated with either oral antidiabetic drugs or insulin at the time of recruitment. They did not show a history of diabetic ketoacidosis at the onset of diabetes mellitus, nor did they receive insulin treatment within 1 year of diagnosis. All of these patients were invited to participate in a health examination and a total of 610 patients (268 men and 342 women) (78.5%) actually participated. The distribution of age and gender between those who did not participate and those who participated were not different significantly. For those who did not participate and those who participated, the respective age was $62.0 \pm 10.6$ years and $63.3 \pm 10.8$ years, respectively; and the respective percentage of men was 42.5% and 43.9%. In order to evaluate the lipid abnormalities associated with UAER without the influence of potential confounders, the subjects recruited into the present study were selected from the 610 subjects based on the following stringent criteria: (*1*) nonsmoker and nonconsumer of alcoholic beverages; (*2*) no history of hypertension and not taking any antihypertensive agent; (*3*) no history or symptoms of congestive heart failure and not receiving treatment for such; (*4*) no use of lipid-lowering agents, antibiotics, hormone replacements, or vitamin supplements; (*5*) normal renal function [blood urea nitrogen (BUN) $\leq$8.6 mmol/L (24 mg/dL) and serum creatinine $\leq$106.1 μmol/L (1.2 mg/dL)]; and (*6*) no acute illness or fever. As a result, a total of 275 patients (122 men and 153 women) aged $60.6 \pm 11.1$ years were recruited.

### Measurements of albumin-to-creatinine (ACR) and calculation of creatinine clearance

The subjects were advised not to participate in vigorous physical activity one day before the examination. Urinary specimen and blood samples were collected in the early morning after the subjects fasted for at least 12 hours. First-void and midstream urine was collected; this was followed by venous blood sampling. The concentration of urine albumin was quantitatively measured by means of particle-enhanced turbidimetric immunoassay (Biolatex, Logrono, Spain). The urine creatinine concentration was measured after 10× dilution on an automatic biochemistry analyzer (Cobas Mira S) (Roche Diagnostica, Basel, Switzerland) with reagents obtained from Randox Laboratories Ltd. (Antrium, UK). ACR was calculated by dividing the urinary albumin concentration in micrograms by the urinary creatinine concentration in milligrams. An ACR $\geq$30 μg/mg was defined as albuminuria, and <30 μg/mg as normoalbuminuria. Creatinine clearance (mL/min) was calculated from the Cockcroft-Gault formulae as: [(140 − age in years) ∗ body weight in kg]/(72 ∗ serum creatinine in mg/dL) [16]. For women, the calculated values were multiplied by 0.85 [16].

### Measurements of lipid parameters

Serum samples were used to determine total cholesterol, triglycerides, HDL cholesterol, and LDL cholesterol levels on an automatic biochemistry analyzer (Cobas Mira S) (Roche Diagnostica) with reagents obtained from Randox Laboratories Ltd. Serum ApoA1 and ApoB were measured with reagents obtained from Raichem SPIA (Reagents Applications Inc., San Diego, CA, USA). A tenfold dilution was made before assay if the serum sample was turbid or triglyceride level was >4.48 mmol/L (400 mg/dL).

Non-HDL cholesterol was calculated as total cholesterol minus HDL cholesterol. The subjects were divided into four phenotypes based on the levels of triglyceride (<1.5 or $\geq$1.5 mmol/L) and ApoB (<1.2 or $\geq$1.2 g/L) as normotriglyceride/normo-ApoB, hypertriglyceride/normo-ApoB, normotriglyceride/hyper-ApoB, and hypertriglyceride/hyper-ApoB. The cutoffs followed

those used by Sniderman et al [17] in a previous study. The triglyceride cutoff was chosen because small dense LDL particles become common above this value [18]. The ApoB cutoff was applied because this level was used in the Framingham Study [19] and the Quebec Cardiovascular Study [20] for risk classification. Both of these two cutoffs are also close to the 75th percentiles of triglyceride and ApoB in the general population of Taiwan in a community study [21].

### Measurements of potential confounders

Age, gender, body mass index, diabetic duration, systolic blood pressure, diastolic blood pressure, and hemoglobin $A_{1c}$ ($HbA_{1c}$) were treated as potential confounders.

Blood pressure was measured on the right arm after 20 minutes rest on a sitting position with a standard mercury sphygmomanometer by the auscultatory method between 8:00 a.m. and 10:00 a.m. The first perception of successive sounds (Korotkoff phase I) was taken as systolic blood pressure and the complete disappearance of sound (Korotkoff phase V) was taken as diastolic blood pressure. Body height in centimeters (cm) and body weight in kilograms (kg) were measured with light clothes and bare feet. Body mass index was calculated as body weight in kg divided by the square of body height in meters. $HbA_{1c}$ was measured by means of boronate affinity chromatography with reagents obtained from the Primus Corporation (Primus CLC385, Kansas City, MO, USA).

### Statistical analyses

Because the distribution of ACR was highly skewed, the natural logarithm of ACR (ln ACR) was used for statistical analyses. Continuous variables were expressed as the mean ± standard deviation (SD), and categorical variables, as percentages. $P < 0.05$ was considered to indicate a statistically significant difference.

The measured lipid parameters (i.e., total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ApoA1, and ApoB) and the calculated non-HDL cholesterol were divided into quartiles and the prevalences of albuminuria among the quartiles of these parameters were tested by linear test for trend.

Differences in the baseline characteristics between the normoalbuminuric and albuminuric groups were tested by using either the $\chi^2$ test or the Student $t$ test. Correlation coefficients between ln ACR and the continuous potential confounders were generated. Age and the variables found to be associated with ln ACR or albuminuria in the above analyses with $P$ values <0.1 were adjusted in further analyses of the correlation coefficients between ln ACR and the lipid parameters and in the multiple logistic regression and linear regression models, performed in separate genders.

The lipid parameters and ln ACR among the four phenotypes were compared by one-way analysis of variance (ANOVA) followed by multiple comparison test using least significant difference (LSD). The frequencies of the four phenotypes in patients with normoalbuminuria and albuminuria were tested by chi-square test. The prevalences of albuminuria in the four phenotypes in all patients and in either gender were tested by linear test for trend. Adjusted odds ratios for albuminuria in the four phenotypes using the normotriglycerides/normo-ApoB group as reference were estimated through logistic regression.

## RESULTS

Among the 275 patients, 152 had normoalbuminuria and the other 123 had albuminuria. Comparisons of the baseline characteristics between the normoalbuminuric and albuminuric groups are shown in Table 1. The albuminuric group was characterized by significantly higher levels of systolic blood pressure, total cholesterol, ApoB, and non-HDL cholesterol. For the prevalences of albuminuria among the four quartiles of lipid parameters, only ApoB and non-HDL cholesterol showed significant linear test for trend and they are illustrated in Figure 1.

In the correlation coefficient analyses between ln ACR and the continuous potential confounders, ln ACR was correlated with systolic blood pressure ($\gamma = 0.124$, $P < 0.05$) and $HbA_{1c}$ ($\gamma = 0.100$, $P < 0.10$) with $P$ values <0.10, and the $P$ values for all of the other correlation coefficients were >0.10. In the following analyses evaluating the association between UAER and lipid parameters, age, systolic blood pressure, and $HbA_{1c}$ were adjusted.

In the correlation coefficient analyses between ln ACR and the lipid parameters after adjusting for age, systolic blood pressure, and $HbA_{1c}$, ln ACR was correlated significantly with total cholesterol, ApoB, and non-HDL cholesterol in all subjects ($\gamma = 0.1422$, 0.1949, and 0.1580, respectively) and in the diabetic men ($\gamma = 0.1948$, 0.2096, and 0.2050, respectively), but only ApoB showed significant correlation with ln ACR in the diabetic women ($\gamma = 0.1779$).

Table 2 shows the odds ratios for albuminuria for the lipid parameters after adjusting for age, systolic blood pressure, and $HbA_{1c}$. Total cholesterol, ApoB, and non-HDL cholesterol showed significant adjusted odds ratios for all subjects and for the diabetic men. For the diabetic women, only ApoB showed significant odds ratio.

Table 3 shows the standardized regression coefficients for ln ACR estimated by the lipid parameters after adjusting for age, systolic blood pressure, and $HbA_{1c}$. The standardized regression coefficients for total cholesterol, ApoB, and non-HDL cholesterol were significant for all subjects and for men, but only ApoB was significant for women.

**Table 1.** Baseline characteristics

| Characteristics | Total | Normoalbuminuria | Albuminuria |
|---|---|---|---|
| Number | 275 | 152 | 123 |
| Age *years* | 60.6 ± 11.1 | 59.9 ± 10.3 | 61.5 ± 12.0 |
| Gender (% men) | 44.4 | 46.1 | 42.3 |
| Body mass index $kg/m^2$ | 24.5 ± 3.3 | 24.4 ± 3.3 | 24.6 ± 3.2 |
| Diabetic duration *years* | 11.0 ± 7.3 | 10.7 ± 7.0 | 11.4 ± 7.7 |
| Systolic blood pressure *mm Hg* | 127.8 ± 14.2 | 125.9 ± 14.9 | 130.2 ± 12.9[a] |
| Diastolic blood pressure *mm Hg* | 76.2 ± 8.9 | 75.7 ± 8.4 | 76.8 ± 9.5 |
| $HbA_{1c}$% | 7.7 ± 1.7 | 7.6 ± 1.7 | 7.9 ± 1.8 |
| Total cholesterol *mmol/L* | 5.25 ± 1.02 | 5.11 ± 1.00 | 5.42 ± 1.03[a] |
| Triglycerides *mmol/L* | 1.79 ± 1.16 | 1.70 ± 1.07 | 1.90 ± 1.26 |
| HDL cholesterol *mmol/L* | 1.29 ± 0.39 | 1.33 ± 0.41 | 1.26 ± 0.36 |
| LDL-cholesterol *mmol/L* | 2.93 ± 0.77 | 2.87 ± 0.76 | 3.00 ± 0.77 |
| ApoA1 *g/L* | 1.43 ± 0.33 | 1.42 ± 0.33 | 1.44 ± 0.34 |
| ApoB *g/L* | 1.14 ± 0.34 | 1.06 ± 0.29 | 1.23 ± 0.37[b] |
| Non-HDL cholesterol *mmol/L* | 3.95 ± 0.98 | 3.78 ± 0.96 | 4.16 ± 0.98[b] |
| Calculated creatinine clearance *mL/min* | 71.5 ± 25.8 | 71.6 ± 21.1 | 71.2 ± 30.7 |

Abbreviations are: $HbA_{1c}$, hemoglobin $A_{1c}$; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.
[a] $P < 0.05$; [b] $P < 0.01$.

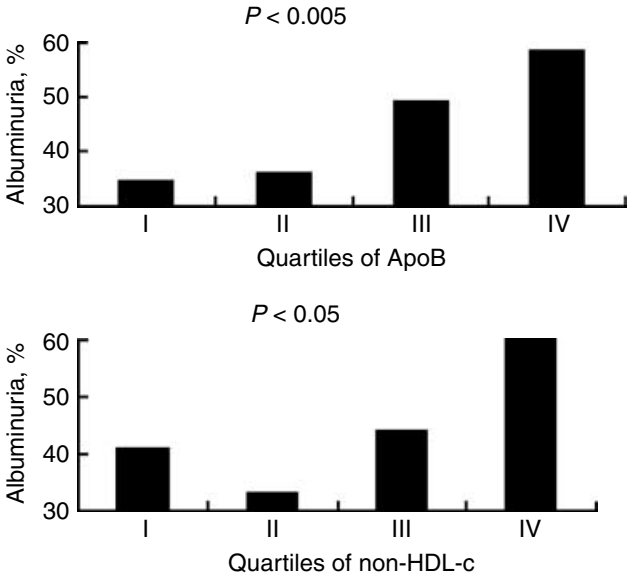


**Fig. 1. Prevalences of albuminuria by quartiles of apolipoprotein B (ApoB) and non-high-density lipoprotein cholesterol (HDL-c).**

Table 4 shows the levels of lipid parameters and ln ACR by the four phenotypes and the frequency distribution and adjusted odds ratios for albuminuria by the four phenotypes. In patients with normoalbuminuria and albuminuria, respectively, 26.3% and 50.4% of the patients had hyper-ApoB disregard the level of triglycerides. All of the lipid parameters differed significantly among the four phenotypes and ln ACR increased accordingly.

## DISCUSSION

The main findings of this study suggested that, among the lipid parameters, only ApoB had the closest association with increased UAER in both the diabetic men and the diabetic women (Tables 2 to 4). Prevalences of albuminuria increased significantly with increasing quartiles of ApoB (Fig. 1) and the association between ApoB and increased UAER was consistently shown in the multiple regression models, either when UAER was expressed as a categorical variable of albuminuria in the logistic regression model (Table 2) or as a continuous variable of ln ACR in multiple linear regression (Table 3). Although quartiles of non-HDL cholesterol also showed significant test for trend for its association with the prevalences of albuminuria, the association was not as remarkable as with ApoB (Fig. 1). Total cholesterol and non-HDL cholesterol were also significantly associated with albuminuria (Table 2) or ln ACR (Table 3), but the odds ratio for ApoB was substantially higher than for non-HDL cholesterol or total cholesterol (Table 2); and the degree of association as expressed by the standardized regression coefficient was also highest for ApoB (Table 3). This finding conformed to a Japanese study showing that type 2 diabetic patients who progressed from normoalbuminuria to microalbuminuria after 2 years had significantly higher baseline ApoB [12]. Conventional practice is to quantitate lipoproteins by their lipid moieties and LDL cholesterol has always been regarded as the cornerstone of disease association and treatment guideline [14]. However, LDL cholesterol was not found to be a good indicator for albuminuria in this study (Tables 1 to 3). It should be pointed out that measurement of LDL cholesterol concentration per se has neglected the impact of other highly atherogenic particles such as VLDL, IDL, and lipoprotein(a) [13]. It is the number of all atherogenic lipoprotein particles and not only the concentration of cholesterol in the LDL particles that contribute to the development of atherosclerosis. Therefore, LDL cholesterol is not as good an indicator for the whole number of atherogenic particles as ApoB is [13]. Although the NCEP-ATP III recommended the calculation of non-HDL cholesterol as a surrogate marker for ApoB [14], it is evident that total

**Table 2.** Odds ratios for albuminuria after adjusting for age, systolic blood pressure, and hemoglobin $A_{1c}$

| Lipid parameters | Total ($N = 275$) | Men ($N = 122$) | Women ($N = 153$) |
|---|---|---|---|
| Total cholesterol | 1.334 (1.041–1.709)[a] | 1.525 (1.008–2.307)[a] | 1.214 (0.885–1.666) |
| Triglycerides | 1.181 (0.950–1.469) | 1.057 (0.726–1.539) | 1.236 (0.932–1.639) |
| HDL cholesterol | 0.618 (0.325–1.175) | 0.749 (0.278–2.015) | 0.519 (0.213–1.269) |
| LDL cholesterol | 1.219 (0.885–1.680) | 1.403 (0.845–2.329) | 1.119 (0.733–1.708) |
| ApoA1 | 1.189 (0.569–2.486) | 1.267 (0.427–3.753) | 1.071 (0.379–3.023) |
| ApoB | 4.517 (2.052–9.946)[b] | 5.998 (1.619–22.219)[b] | 3.836 (1.416–10.394)[b] |
| Non-HDL cholesterol | 1.490 (1.143–1.942)[b] | 1.610 (1.061–2.444)[a] | 1.382 (0.977–1.956) |

Abbreviations are: HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.
[a]$P < 0.05$; [b]$P < 0.01$.

**Table 3.** Standardized regression coefficients for natural logarithm of albumin-to-creatinine ratio after adjusting for age, systolic blood pressure, and hemoglobin $A_{1c}$

| Lipid parameters | Total ($N = 275$) | Men ($N = 122$) | Women ($N = 153$) |
|---|---|---|---|
| Total cholesterol | 0.141[a] | 0.195[a] | 0.088 |
| Triglycerides | 0.094 | 0.050 | 0.103 |
| HDL cholesterol | −0.024 | −0.023 | −0.037 |
| LDL cholesterol | 0.093 | 0.114 | 0.072 |
| ApoA1 | 0.101 | 0.088 | 0.084 |
| ApoB | 0.194[b] | 0.214[a] | 0.174[a] |
| Non-HDL cholesterol | 0.157[b] | 0.207[a] | 0.109 |

Abbreviations are: HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA1, apolipoprotein A1; ApoB, apolipoprotein B.
[a]$P < 0.05$; [b]$P < 0.01$.

cholesterol or this surrogate marker was associated with albuminuria or ln ACR only in the diabetic men but not in the diabetic women (Tables 2 and 3). The cause for this sexual discrepancy is unknown, but the results suggested a need for the measurement of ApoB rather than total cholesterol or the surrogate marker of non-HDL cholesterol.

The positive association between triglycerides and the progression to microalbuminuria in the Japanese study [12] was not similarly observed in the present study. Neither triglyceride was associated with progression of human chronic renal insufficiency in the study by Samuelsson et al [11]. However, the results supported that the phenotype classification based on triglycerides and ApoB could better identify the patients' risk of albuminuria (Table 4). Among the four phenotypes, hypertriglycerides/hyper-ApoB was associated with the highest risk, patients with normotriglycerides/hyper-ApoB had an intermediate risk, and the risk in patients having normo-ApoB is the lowest, disregard the level of triglycerides (Table 4). Although the underlying pathophysiologic mechanisms are not fully known, the results are compatible with previous reports showing intact or partially metabolized triglyceride-rich but not cholesterol-rich ApoB-containing lipoproteins of VLDL, IDL, and LDL fractions being more closely associated with rapid loss of renal function [22, 23]. In patients with normotriglycerides, if ApoB was not measured, the patients at high risk of albuminuria associated with normotriglycerides/hyper-ApoB would not be identified (Table 4). A measurement of ApoB in patients with hypertriglycerides could also provide more information about their risk of albuminuria, because the adjusted odds ratio associated with hypertriglycerides/hyper-ApoB phenotype was still higher than that of the hypertriglycerides/normo-ApoB phenotype (Table 4). Although not statistically significant (probably due to the small case number in the group of normotriglycerides/hyper-ApoB), the trend showed that in patients with hyper-ApoB, a simultaneous increase in triglycerides (the hypertriglycerides/hyper-ApoB phenotype) might suggest a higher risk of albuminuria than those with normotriglycerides (the normotriglycerides/hyper-ApoB phenotype) (Table 4).

The cause/effect relationship between the lipid abnormalities and increased UAER cannot be easily discerned in this study. It is well known that dyslipidemia can be resulted from renal disease, because dysregulation of lipid metabolism and dyslipidemia can well be demonstrated in animals following induction of proteinuria with renal insufficiency [24–26]. Although the underlying pathophysiologic mechanisms have not yet been fully elucidated, increased hepatic synthesis and decreased catabolism of lipoproteins and their delayed removal from plasma have been documented in both animals and humans [27–33]. However, what was investigated in this study was not advanced renal disease, it was the early stage of albuminuria that was investigated because all patients with abnormal renal function had been excluded from the study. The study of Kashiwazaki et al [35] suggested that the widespread endothelial damage in type 2 diabetic patients with microalbuminuria might lead to decreased release of lipoprotein lipase (LPL) moiety bound to the endothelium resulting in an impaired catabolism of triglyceride-rich lipoproteins. Although decreased LPL activity will slow down triglyceride clearance leading to hypertriglycerides, it can not lead to an elevated ApoB if LDL clearance is not markedly reduced or in combination with a markedly enhanced VLDL production. Whether early renal problem in the stage of increased UAER as investigated in the present study could cause increased secretion of VLDL particle from the liver is not known, but in doubt.

**Table 4.** Comparisons among the four phenotypes classified by triglycerides and apolipoprotein B

| | A Normotriglycerides/ normo-ApoB | B Hypertriglycerides/ normo-ApoB | C Normotriglycerides/ hyper-ApoB | D Hypertriglycerides/ hyper-ApoB | *P* value[g] |
|---|---|---|---|---|---|
| Number% | | | | | *P* (chi-square test) |
| Total | 105 (38.2%) | 68 (24.7%) | 35 (12.7%) | 67 (24.4%) | <0.001 |
| Normoalbuminuria | 68 (44.7%) | 44 (28.9%) | 16 (10.5%) | 24 (15.8%) | |
| Albuminuria | 37 (30.1%) | 24 (19.5%) | 19 (15.4%) | 43 (35.0%) | |
| Total cholesterol *mmol/L* | 4.82 ± 0.93 | 4.94 ± 0.83 | 5.78 ± 0.87 | 5.94 ± 0.94 | <0.001[b,c,d,e] |
| Triglycerides *mmol/L* | 0.96 ± 0.30 | 2.45 ± 0.93 | 1.04 ± 0.29 | 2.81 ± 1.27 | <0.001[a,c,d,e,f] |
| HDL cholesterol *mmol/L* | 1.44 ± 0.41 | 1.14 ± 0.36 | 1.32 ± 0.31 | 1.20 ± 0.34 | <0.001[a,c,d] |
| LDL cholesterol *mmol/L* | 2.73 ± 0.71 | 2.63 ± 0.63 | 3.41 ± 0.67 | 3.28 ± 0.78 | <0.001[b,c,d,e] |
| ApoA1 *g/L* | 1.40 ± 0.33 | 1.31 ± 0.35 | 1.53 ± 0.33 | 1.54 ± 0.28 | <0.001[b,c,d,e] |
| ApoB *g/L* | 0.92 ± 0.17 | 0.95 ± 0.15 | 1.47 ± 0.23 | 1.50 ± 0.27 | <0.001[b,c,d,e] |
| Non-HDL cholesterol *mmol/L* | 3.38 ± 0.82 | 3.80 ± 0.74 | 4.46 ± 0.77 | 4.74 ± 0.90 | <0.001[a,b,c,d,e] |
| Ln ACR | 3.14 ± 1.16 | 3.17 ± 1.12 | 3.64 ± 1.31 | 3.88 ± 1.24 | <0.001[b,c,e] |
| Albuminuria% | | | | | *P* (trend test) |
| Total | 35.2 | 35.3 | 54.3 | 64.2 | <0.001 |
| Men | 31.1 | 34.3 | 53.3 | 66.7 | 0.002 |
| Women | 38.2 | 36.4 | 55.0 | 62.5 | 0.01 |
| Adjusted odds ratio[h] | | | | | |
| Total | 1.00 | 1.04 (0.54–2.00) | 2.25 (1.02–5.00) | 3.38 (1.75–6.53) | |
| Men | 1.00 | 1.15 (0.44–3.01) | 2.73 (0.80–9.31) | 4.26 (1.46–12.40) | |
| Women | 1.00 | 0.96 (0.39–2.37) | 2.02 (0.70–5.84) | 2.77 (1.18–6.46) | |

Abbreviations are: Normotriglycerides, triglycerides <1.5 mmol/l; hypertrigylcerides, triglycerides ≥1.5 mmol/L; normo-apolipoprotein B (ApoB), ApoB <1.2 g/L; hyper-ApoB, ApoB ≥1.2 g/L; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoA1, apolipoprotein A1.

Multiple comparison test with least significant difference are significant for [a]A vs. B; [b]A vs. C; [c]A vs. D; [d]B vs. C; [e]B vs. D; [f]C vs. D.

[g]*P* by one-way analysis of variance unless otherwise specified.

[h]Odds ratios for albuminuria were adjusted for age, systolic blood pressure, and $HbA_{1c}$.

On the other hand, elevated serum lipid concentration may cause impairment and progression in renal function. For example, ApoB was associated with a declining GFR in an early study [10]. The same group later reported that renal dyslipidemia was predominantly associated with the accumulation of ApoB-containing lipoproteins in both sclerotic and nonsclerotic glomeruli [11]. Glomerular cells possess LDL receptors, and mesangial and glomerular epithelial cells can internalize IDL by means of both receptor- and nonreceptor-mediated mechanisms [11]. A series of lipoprotein-induced cellular events occur in the glomeruli, similar to the vascular effects of atherosclerosis [34]. The infiltration of atherogenic lipoproteins into the glomerular endothelium and mesangial cells can initiate a cascade of events, including adhesion molecule expression, monocyte chemoattractant production, and release of reactive oxygen species, that lead to early glomerular injury [34]. Therefore, although dyslipidemia and renal dysfunction may perpetuate each other, leading to accelerated atherosclerosis and renal insufficiency, dyslipidemia leading to renal dysfunction seems to be much more likely in the early stage with the more profound evidence from the prospective follow-up studies [10–12] and the biologic plausibility [34]. However, much more investigations are required to settle this controversial issue of cause and effect.

One strength of this study is the exclusion of many of the potential confounders at the stage of patient recruitment, making the two groups of patients with and without albuminuria more comparable. Residual confounding effects were further considered and adjusted during the stage of statistical analyses. The findings also suggested that the lipid abnormalities associated with increased UAER could not be ascribed to a change in the GFR, because the normoalbuminuric and albuminuric groups had comparable calculated creatinine clearance (Table 1) and ln ACR was not correlated significantly with the calculated creatinine clearance (data not shown). In further analyses, even when calculated creatinine clearance was additionally adjusted for, the results were similar (data not shown). The lack of an association between ln ACR and calculated creatinine clearance was not surprising, because patients with elevated creatinine levels had already been excluded from the study at recruitment.

However, the cross-sectional design of this study was not sufficient to confirm a causal relationship between the lipid abnormalities and albuminuria or elevated UAER. Since the patient cohort of the diabetic clinic recruited in this study might not necessarily be representative for patients not attending the diabetic clinic of this hospital, selection bias remains possible. Therefore, the extension of the results of this study to type 2 diabetic patients in general remains to be confirmed. The cutoffs used to define the phenotypes are somewhat arbitrary, but this is always the case. These cutoffs have been applied previously by other investigators [17] and are the values used by the Quebec Cardiovascular Study [20] and the Framingham Study [19] to define increased risk. These values are also close to the 75th percentiles of our population [21]. Therefore, the use of these cutoff values avoided the possible bias associated with the use of other self-selected criteria and was surely much more reasonable.

## CONCLUSION

Among the lipid parameters of total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol, ApoA1, ApoB, and non-HDL cholesterol, only ApoB is significantly associated with albuminuria or ln ACR in both genders. The use of non-HDL cholesterol as a surrogate marker for ApoB might not be applicable in the diabetic women. Patients with the phenotype of hypertriglycerides/hyper-ApoB have the highest risk of albuminuria.

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